REMARKS

Claims 93-120 and 144-151 are all the claims pending in the application.

Claims 144, 146, 148 and 150 have been amended to correct an obvious misspelling.

No new matter has been added. Entry of this amendment is respectfully requested.

I. Rejection of Claims Under 35 U.S.C. §112

At paragraphs 3-4 of the Office Action, claim 120 is rejected under 35 U.S.C. §112, first paragraph, as lacking written description support in the specification.

In paragraph 3, the Examiner states that claim 120 is drawn to a *synergistic* combination of (1) taxol with (2) at least one immunoconjugate of maytansinoid conjugated to a monoclonal antibody which binds to an antigen expressed by a cancer cell. The Examiner further states that the specification only provides support for the combination of huN901-DM1/paclitacel and huC242-DM1/paclitaxel for eliciting a synergistic therapeutic effect. The Examiner asserts that without a specific description of a genus of antibodies which exert a synergistic effect when administered with taxol, the skilled artisan would not assume that the generic combination of antibodies with taxol would exhibit a synergistic effect. The Examiner concludes that claim 120 broadens the scope of the invention as originally filed.

In response to Applicants' arguments (Amendment filed May 5, 2004), the Examiner states in paragraph 4 that "unexpectedly superior results" is not the same as "synergistic." The Examiner contends that a superior result could be attained by the additive effect of each chemotherapeutic agent or the administration of an agent and an immunoconjugate. The Examiner asserts that a synergistic effect, by definition, would be a result that was more than the additive effect of the chemotherapeutic agent and the immunoconjugate.

Applicants note that the Examiner appears to be raising four different points in this rejection, each of which is discussed as follows.

Broadening the scope

The Examiner states that claim 120 broadens the scope of the invention as originally filed.

The Examiner notes that claim 120 includes the following elements:

(a) a synergistic combination

(b) taxol

(c) at least one immunoconjugate comprising:

(i) maytansinoid, and

(ii) a monoclonal antibody

(d) binding of an antigen expressed by a cancer cell by the immunoconjugate.

As to (a), it is indicated at page 2, lines 4-6, at page 3, lines 6-7, and at page 22, lines 3-7, of the specification that the present invention encompasses a combination of a chemotherapeutic agent and an immunoconjugate that produces "unexpectedly superior results." As stated at page 33, line 29, at page 34, line 23, at page 35, line 19, and other locations in the specification, an example of what is meant by "unexpectedly superior results" includes "synergistic." Therefore, it is clear that a "synergistic combination" is supported by the specification.

As to (b), at page 3, lines 6-8, it is stated that the chemotherapeutic agent may be a taxane, and at page 24, lines 3-4, it is stated that the taxane may be paclitaxel (taxol).

As to (c), at page 3, lines 10-15, it is stated that the immunoconjugate may comprise a maytansinoid as the therapeutic agent and a monoclonal antibody as the cell binding agent.

As to (d), original claim 12 provides support for the binding of the immunoconjugate to an antigen expressed by a cancer cell.

For these reasons, Applicants respectfully assert that each element of claim 120 is clearly supported by the specification, and that the claim does not broaden the scope of the invention.

Genus of antibodies

The Examiner argues that without a specific description of the genus of antibodies which exert a synergistic effect when administered with taxol, the skilled artisan would not assume that the generic combination of antibodies with taxol would exhibit a synergistic effect.

Before commenting specifically on this point of the Examiner's rejection, Applicants believe that it might be helpful to provide the Examiner with a brief overview of the subject matter of the invention.

The instant invention is based on the unexpected finding that improved results in the treatment of cancer is possible through the treatment of a patient with a combined therapy comprising a chemotherapeutic agent and an immunoconjugate. Such treatment comprises administering to a patient at least one chemotherapeutic agent, which may be selected from agents known to one skilled in the art and described in the specification, and an immunoconjugate, which comprises a drug (such as a maytansinoid) linked to cell binding agent (such as an antibody). The purpose of the cell binding agent is in the targeting of the attached drug to a specific destination, e.g., the tumor cell being targeted. Once the drug reaches its destination, it is presented to the cell through the binding of the cell binding agent to the cell.

While the drug itself can modulate growth of the targeted cancer cell or kill the cell, its modulating or killing activity is enhanced when the targeted cell is also treated with a

chemotherapeutic agent. Thus, the targeted cancer cell is being treated by a combination of two drugs, one of which is a chemotherapeutic agent and the other of which is a drug delivered to the cell as an immunoconjugate. The identity of the cell binding agent (e.g., antibody) is not particularly important, other than that it needs to specifically recognize and bind the targeted cell. Selection of cell binding agent depends on the particular cell population that is to be targeted.

By means of experimental examples, Applicants have shown that when the chemotherapeutic agent (e.g., paclitaxel) or an immunoconjugate (e.g., huN901-DM1) is used alone, the tumor cells being targeted by these drugs exhibit some growth modulation, e.g., a modest anti-tumor effect with a tumor growth delay of 4 days in mice (see Example 2, page 33, of the specification). However, when the tumors were treated with a combination of the two agents, the tumor disappeared with complete regression lasting 58 days. Moreover, there was no evidence of toxicity in the animals.

That the above results are consistent and reproducible is underscored by the fact that other chemotherapeutic agents, such as cisplatin, etoposide, decetaxel and topotecan, in conjunction with an immunoconjugate (e.g.., huN901-DM1 or huC242-DM1) have a similar effect on tumor regression, i.e., when a chemotherapeutic agent or an immunoconjugate is used alone, only a modest anti-tumor effect results, which is remarkably enhanced by the synergistic combination of the two agents together (see Examples 3-7, pages 34-38, of the specification).

As stated in the specification, the unexpectedly superior or remarkably enhanced anti-tumor effect that results from a combinatorial use of a chemotherapeutic agent and an immunoconjugate is brought about by their synergistic interaction, from which an ordinarily skilled artisan can readily infer that a combinatorial use of a chemotherapeutic agent and an

immunoconjugate can have a synergistic effect (see, e.g., page 33, line 29, and Figures 5-10) on tumor growth.

Returning to the rejection, Applicants note that the Examiner's concentration appears to be on the scope of the antibodies used in the combination. As explained above, the antibody is not the cytotoxic portion of the claimed composition. Indeed, any antibody that recognizes an epitope expressed by a cancer cell could likely be used in the invention. As it is not the antibody itself that has a cytotoxic effect on the cancer cells, the identity of the antibody has little bearing on the combination. The skilled artisan would readily recognize that any antibody that binds a cancer cell epitope could be used in the immunoconjugate.

Unexpectedly superior results

The Examiner states that "unexpectedly superior results" is not the same as "synergistic."

As noted above, it is indicated at page 2, lines 4-6, at page 3, lines 6-7, and at page 22, lines 3-7, of the specification, that the present invention encompasses a combination of a chemotherapeutic agent and an immunoconjugate that produces "unexpectedly superior results." As stated at page 33, line 29, at page 34, line 23, at page 35, line 19, and other locations in the specification, an example of what is meant by "unexpectedly superior results" includes "synergistic." Therefore, it is clear that a "synergistic combination" is supported by the specification and that it is an example of an "unexpectedly superior result" as the phrase is used by Applicants.

Only two examples of synergistic combinations

The Examiner states that the specification only provides two examples of synergistic-acting combinations, both of which rely on paclitaxel.

Applicants respectfully note that each of Examples 2-7 demonstrates a synergistic-acting combination. Further, that the chemotherapeutic agents in these examples include non-paclitaxel compounds, namely cisplatin and etoposide (platinum compounds) in Example 3, docetaxel (a taxane) in Example 4, topotecan (a camptothecin) in Example 5, and irinotecan (a camptothecin) in Example 7.

Thus, in contrast to the Examiner's position, the skilled artisan would not "reasonably conclude" that other, non-paclitaxel, combinations "would not be synergistic." Indeed, given the scope of the compounds used in the Examples, the skilled artisan would conclude that a number of different chemotherapeutic agents could be used in combination with a maytansinoid to produce a synergistic combination. It would be apparent to the skilled artisan that as a maytansinoid is used in each of the Examples, that it is the maytansinoid that imparts the synergistic effect to the combination, and that many different chemotherapeutic agents would likely form synergistic combinations with maytansinoids.

In view of these comments, Applicants respectfully assert that claims 120 has adequate written description support in the application as filed, and therefore request reconsideration and withdrawal of this rejection.

II. Rejection of Claims Under 35 U.S.C. §103

A. At paragraph 5 of the Office Action, claims 93-97, 99, 102-110, 112 and 115-119 are rejected under 35 U.S.C. §103(a) as not being patentable over Siegall (1997) in view of Chari (1992).

The Examiner states that Siegall teaches a combination therapy comprising paclitaxel as the chemotherapeutic agent and a Pseudomonas endotoxin linked to a single chain antibody as

the immunoconjugate. The Examiner notes that while the rejected claims recite maytansinoid linked to an antibody as the immunoconjugate, and although Siegall teaches the use of Pseudomonas endotoxin, Chari et al. teaches linking maytansinoids to antibodies. The Examiner contends it would have been *prima facie* obvious to combine the two disclosures to arrive at the claimed invention. The Examiner states that the skilled artisan would have been motivated to combine the two disclosures by the teachings of Chari et al. of an advantage of using protein toxins versus anticancer drugs in immunoconjugates in that protein toxins act catalytically rather than stoichiometrically. The Examiner notes that one of skill in the art would expect that a BR96-sFV-maytansinoid immunotoxin would have a "similar therapeutic potential" as the BR96-sFv-PE40 immunotoxin."

To establish a *prima facie* case of obviousness, an examiner must demonstrate three basic criteria: (1) there must be some suggestion or motivation to combine the prior art references, (2) there must be a reasonable expectation of success in combining the references, and (3) the prior art references must teach or suggest all of the claim limitations.

Applicants respectfully assert that the Examiner has not met the first or second elements.

(i) As to the first element of the test, MPEP §2143.01 states that "obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art." Thus, absent evidence of a "teaching, suggestion, or motivation" to combine Siegall and Chari et al., the Examiner has not established a *prima facie* case of obviousness.

Importantly, as further noted in MPEP §2143.01:

> The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990) (Claims were directed to an apparatus for producing an aerated cementitious composition by drawing air into the cementitious composition by driving the output pump at a capacity greater than the feed rate. The prior art reference taught that the feed means can be run at a variable speed, however the court found that this does not require that the output pump be run at the claimed speed so that air is drawn into the mixing chamber and is entrained in the ingredients during operation. Although a prior art device "may be capable of being modified to run the way the apparatus is claimed, there must be a suggestion or motivation in the reference to do so." 916 F.2d at 682, 16 USPQ2d at 1432.).

While it might be possible to use an immunoconjugate comprising a maytansinoid, as taught by Chari et al., with paclitaxel, as taught by Siegall, the mere fact that the references could be combined does not render the combination obvious unless the prior art "also suggests the desirability of the combination." As with *In re Mills* above, although the combination of Siegall "may be capable of being modified" to use the immunoconjugate of Chari et al., "there must be a suggestion or motivation in the reference to do so."

As further noted in MPEP §2143.01, simply because the reference existed and the modifications would have been within the ordinary skill in the art at the time the claimed invention was made "is not sufficient to establish a prima facie case of obviousness without some objective reason to combine the teachings of the references." As indicated by the Court of Appeals for the Federal Circuit, the level of skill in the art cannot be relied upon to provide the suggestion to combine references. *Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308, 50 USPQ2d 1161 (Fed. Cir. 1999).

The only suggestion or motivation the Examiner points to for combining the references is based on an advantage of using a protein toxin over the use of an anticancer drug. The Examiner has stated on the record that Chari teaches that using protein toxins is advantageous over anticancer drugs in immunoconjugates because the protein toxins act catalytically rather than stoichiometrically. Importantly, however, maytansinoids are not proteins, but instead they are the anticancer drugs referred to in Chari.[1] As such, Chari does not provide support for the Examiner's position that Chari provides a motivation to combine its teachings with that of Siegall. If Chari teaches the advantage of using protein toxins over anticancer drugs in immunoconjugates as the Examiner states, then the skilled artisan would not be motivated to use a maytansinoid (an anticancer drug) in the combination taught by Siegall.

Indeed, Chari et al. teaches away from the claimed combination in that, as stated by the Examiner, protein toxin-based immunoconjugates are better than anticancer drug-based immunoconjugates (such as those using maytansinoids).

As the Examiner has not pointed to any suggestion or motivation to combine the prior art references, either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art, the Examiner has not met the first element of the test.

(ii) The Examiner has also not met the second element of the test, namely, establishing that there exists a reasonable expectation of success in combining the references.

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[1] The Examiner's attention is drawn to formula IV of claim 102 which shows the chemical formula of a maytansinoid, clearly demonstrating that maytansinoids are not proteins. The Examiner's attention is further drawn to page 128, column 1, first paragraph under the heading RESULTS AND DISCUSSION, lines 4-7, where maytansine is discussed in the context of "other anticancer drugs."

The Examiner states that one of skill in the art would recognize that both PE40 (the Pseudomonas endotoxin) and maytansin are protein toxins which act catalytically when internalized by a cell, thus one of skill in the art would expect that a BR96-sFV-maytansinoid immunotoxin would have a similar therapeutic potential as the BR96-sFV-PE40 immunotoxin.

In contrast to the Examiner's position, as noted above maytansinoids are not proteins. Thus, while the Examiner states that there would be a reasonable expectation of success in substitution of one protein toxin for another, as maytansinoids are not proteins, such an expectation would not have existed.

Indeed, the Examiner notes "the advantage of using protein toxins versus anticancer drugs." As PE40 of Siegall is a protein toxin, and maytansinoids are "anticancer drugs", the Examiner's own statement provides support for the fact that the cited art teaches away from the combination recited in the rejected claims.

Applicants also offer the following comments concerning the science behind synergistic combinations. Synergistic behavior between two chemotherapeutic agents is extremely unpredictable, and must be worked out experimentally for each class of chemotherapeutic agents. The reasons for this include the following. For most, if not all, classes of chemotherapeutic agents, the actual biological mechanism, i.e., the entire pathway of action, is not known and therefore it is not known what actions contribute to the therapeutic effect. There are many possible known and unknown mechanisms. The addition of a second agent on the same target increases the complexity of mechanisms to a degree that makes it impossible to predict the outcome, i.e., to predict if the combined effect will be synergistic, additive, or antagonistic.

Therefore, the demonstration that an antibody-endotoxin conjugate is synergistic with paclitaxel, as in Siegall, has no bearing on the effect of an antibody-maytansinoid conjugate with paclitaxel. The mechanism of action of endotoxin is very complex, not entirely understood, and different from the mechanism of action of maytansine, which is also complex and not entirely understood. Further, conjugation of these agents to an antibody adds another level of complexity to the mechanisms, which again will be different for different classes of agents.

Herein, Applications have shown that certain specific antibody-maytansinoid conjugates unexpectedly act synergistically with certain classes of chemotherapeutic agents. The particular chemotherapeutic agents are paclitaxel, docetaxel, cisplatin and etoposid, topotecan and irinotecan. Paclitaxel and docetaxel define the drug class of taxanes, cisplatin defines the class of platinum compounds, irinotecan defines the class of topoisomerase I inhibitors.

In view of these comments, it is clear that the Examiner has not established a reasonable expectation of success in combining the references, and therefore the Examiner has also not met the second element of the test for obviousness.

For these reasons, Applicants respectfully traverse the rejection of the noted claims as being obvious over the combination of Siegall and Chari et al., and request reconsideration and withdrawal of this rejection.

B. At paragraph 6 of the Office Action, claims 93-97, 99, 101-110, 112, 114-119, 144, 146, 148 and 150 are rejected under 35 U.S.C. §103(a) as not being patentable over Liu (1997) in view of Iwasaki (1998), Pegram (1999), Watson (1996) and Schlom (1991).

The Examiner describes the cited references as follows. Liu teaches an immunoconjugate comprising an antibody and a maytansinoid. Iwasaki teaches that

maytansinoids and taxol bind to tubulin at different sites and that taxol promotes microtubule formation. Watson teaches taxol stabilizes microtubules resulting in the growth arrest of cells at G2/M. Pegram teaches that the interaction of two drugs may result in an additive effect, a synergistic effect or an antagonistic effect, and that two drugs targeting the same enzyme or biochemical pathway may compete with one another resulting in an antagonistic interaction. Schlom teaches humanization of murine antibodies.

The Examiner concludes that it would have been *prima facie* obvious to one of ordinary skill in the art to combine the administration of a maytansinoid-based immunoconjugate with taxol. The Examiner states that the skilled artisan would have been motivated to do so with a reasonable expectation of success by Liu, which teaches that limited binding sites exist for its immunoconjugates and the antitubulin mode of action of maytansinoids. The Examiner notes Pegram teaches the administration of two drugs could result in antagonism if the two drugs were targeted to the same molecular mechanism. The Examiner further notes that Liu teaches maytansinoids kill cells by interfering with formation of microtubules, while Iwasaki teaches taxol stabilizes microtubulin and does not bind the same site as vinblastine.

The Examiner further concludes that one of skill in the art would have been motivated to combine the maytansinoid-based immunoconjugate with taxol in order to exert a cytotoxic effect on cells that do not express enough target antigen to "result in accumulation of a sufficient amount of the maytansinoid to be cytotoxic." The Examiner also states that taxol will not compete with maytansinoid in the binding of tubulin due to different binding sites, and thus no antagonistic reaction will result. The Examiner finishes by stating that because the mechanism

of action differs between maytansinoid and taxol, "it is logical to suppose that the combination of the two agents might produce some additive effect."

Applicants again note that to establish a prima facie case of obviousness, an examiner must demonstrate three basic criteria: (1) there must be some suggestion or motivation to combine the prior art references, (2) there must be a reasonable expectation of success in combining the references, and (3) the prior art references must teach or suggest all of the claim limitations.

Applicants respectfully contend that the Examiner has not met the first or second elements.

(i) As to the first element, MPEP §2143.01 states that "obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art." Thus, absent evidence of a "teaching, suggestion, or motivation" to combine the cited references, the Examiner has not established a *prima facie* case of obviousness.

The Examiner has not pointed to any specific teaching or suggestion in the cited references that teaches or suggests combining the cited references. Nor is there an implicit or explicit motivation to combine the cited references. At the bottom of page 7 of the Office Action, the Examiner merely states that the skilled artisan would be motivated "by the teachings of Liu et al. on the limited expression of target antigens on tumor cells which restricts the amount of drug delivered as an impediment to the clinical efficacy of immunoconjugates and the

teachings of Liu et al on the antitubulin mode of action of maytansinoids, the delivered drug." This is not an implicit or explicit motivation. It is merely a statement of the problems associated with a particular group of immunoconjugates.

The Examiner goes on to state at page 8 that "[o]ne of skill in the art would be motivated to combine the C242-DM1 immunotoxin with taxol in order to exert a cytotoxic effect on cells which do not express enough of the CanAg targeted by the C242 antibody to result in accumulation of a sufficient amount of the maytansinoid to be cytotoxic." While the Examiner is stating her opinion as to what would happen if the teachings of Liu and those of Watson and Iwasaki were combined (cytotoxic effect on cells), she has not indicated an implicit or explicit motivation to combine the references. There are likely thousands of compounds that exert cytotoxic effects on cells. The Examiner has not provided a motivation to combine the specific references cited in the Office Action.

In support of her position, the Examiner states at page 8 that:

> One of skill in the art would recognize that in the cells which express enough of the CanAg to internalize the C242-DM1 immunoconjugate to the extent that sufficient maytansinoid will accumulate and exert a cytotoxic effect, taxol will not compete with maytansinoid in the binding of tubulin because taxol and maytansinoid bind to different sites on tubulin, and thus, the administration of taxol in combination with C242-DM1 would not result in an antagonistic effect on said cells.

There is no support for two of the Examiner's statements. First, the Examiner states that that "taxol will not compete with maytansinoid in the binding of tubulin because taxol and maytansinoid bind to different sites on tubulin." The Examiner cites to no evidence in support of her position that these two molecules would not compete for binding. The Examiner has provided no indication of the size of the molecules, the size of the protein they bind, the exact

binding location of the molecules on the protein or the steric effects on the protein that result from the binding of one or the other of the molecules. Indeed, it would be more reasonable to expect that molecules do interfere with each other's binding to the same protein, even if the location of binding might be different.

As stated in MPEP §2144.03, "in limited circumstances, it is appropriate for an examiner to take official notice of facts not in the record or to rely on 'common knowledge' in making a rejection, however such rejections should be judiciously applied."

As further stated in MPEP §2144.03:

> It would not be appropriate for the examiner to take official notice of facts without citing a prior art reference where the facts asserted to be well known are not capable of instant and unquestionable demonstration as being well-known. For example, assertions of technical facts in the areas of esoteric technology or specific knowledge of the prior art must always be supported by citation to some reference work recognized as standard in the pertinent art. *In re Ahlert*, 424 F.2d at 1091, 165 USPQ at 420-21. See also *In re Grose*, 592 F.2d 1161, 1167-68, 201 USPQ 57, 63 (CCPA 1979) ("[W]hen the PTO seeks to rely upon a chemical theory, in establishing a prima facie case of obviousness, it must provide evidentiary support for the existence and meaning of that theory.").

Whether "taxol will compete with maytansinoid in the binding of tubulin" is not a fact that is "capable of instant and unquestionable demonstration as being well-known."

Second, the Examiner states that "the administration of taxol in combination with C242-DM1 would not result in an antagonistic effect on said cells." Whether or not there would be an antagonistic effect is not a fact that is "capable of instant and unquestionable demonstration as being well-known."

Finally, the Examiner concludes at page 8 that "[b]ecause the mechanisms of action of these two agents differ with respect to the molecular basis by which they induce an anti-mitotic

effect, it is logical to suppose that the combination of the two agents might produce some additive effect." Applicants respectfully contend that the Examiner's supposition is merely that, a guess as to what might be the result of the interaction of the two agents. Such a statement does nothing to support the Examiner's position that there was motivation to combine the specific references cited as the basis for this rejection. The Examiner appears to improperly be using hindsight to make conclusions regarding the potential results of combining the cited documents.

For these reasons, the Examiner has not established that there was a teaching, suggestion or motivation to combine the cited references as a basis for the instant obviousness rejection of the claims.

(ii) As to the second element of the obviousness test, the Examiner has not established that there exists a reasonable expectation of success in combining the references. The Examiner states at page 6 that "Pegram et al. teach that the interaction between two drugs may result in an additive effect, a synergistic effect, or an antagonistic effect. Pegram et al. point out that two drugs targeting the same enzyme or biochemical pathway may compete with one another resulting in an antagonistic interaction (page 2242, first column, lines 6-9)."

As noted by the Examiner, Pegram teaches that "the interaction between two drugs may result in an additive effect, a synergistic effect, or an antagonistic effect." Thus, Pegram is teaching that two very different results are possible for any particular combination, i.e., a synergistic effect or an antagonistic effect. Pegram does not provide any expectation of success in combining any two drugs, let alone a *reasonable expectation* of success.

In fact, Pegram teaches away from the instant invention in that it states that two drugs targeting the same enzyme or biochemical pathway may compete with one another resulting in

an antagonistic interaction. As the Examiner has indicated, both maytansinoid and taxol target the same biochemical pathway, i.e., the formation of microtubules. While the Examiner has cited to support that maytansinoid and taxol may bind to separate sites on the tubulin protein, the formation of microtubules is a specific and discrete biochemical pathway. Furthermore, the Examiner has not cited to evidence to confirm that the two molecules recognize separate cites on the protein. The Examiner states at page 6 of the Office Action that Watson teaches that vinblastine and taxol bind to tubulin at different sites. The Examiner also states that Watson teaches that the maytansinoid binding site "partially overlaps" the vinblastine binding site. It is possible that because the maytansinoid site only "partially overlaps" the vinblastine site that it also "partially overlaps" the taxol binding site. The Examiner does not provide any evidence as to whether the maytansinoid binding site and the taxol binding sites are indeed separated. Thus, in the absence of any evidence to the contrary cited by the Examiner, one of ordinary skill in the art reviewing Pegram would come to a conclusion opposite that of the Examiner, that the because the two drugs target the same protein, and thus the same biochemical pathway, they would have antagonistic effects on each other.

Therefore, in contrast to the Examiner's position, there would not have been a reasonable expectation of success in combining the cited references.

For these reasons, Applicants respectfully traverse the rejection of the noted claims as being obvious over the cited combination of references, and request reconsideration and withdrawal of this rejection.

C. At paragraph 7 of the Office Action, claims 93-97, 99, 101-110, 112, 114-119 and 144-151 are rejected under 35 U.S.C. §103(a) "as being unpatentable over as applied to claims

93-97, 99, 101-110, 112, 114-119, 144, 146, 148 and 150 above, and further in view of Chari (1992).

The Examiner states that Chari teaches the chemical synthesis of the structures of claims 102-105, 115-117, 120, 145, 147, 149 and 150. The Examiner further states that it would have been *prima facie* obvious to make the immunoconjugates comprising the maytansinoids synthesized by Chari. The Examiner explains that one of skill in the art would have been motivated to do so by the teachings of Chari on the high therapeutic index afforded by maytansinoid toxins relative to chemotherapeutic agents.

Applicants first note that the rejection is incomplete as the Examiner does not indicate what reference(s) is being combined with Chari in the rejection. As Chari alone does not teach a combination comprising an immunoconjugate and a chemotherapeutic agent, as recited in the rejected claims, the claims are not obviousness in view of Chari.

Applicants understand that the Examiner may have intended to cite to Liu (1997), Iwasaki (1998), Pegram (1999), Watson (1996) and/or Schlom (1991), in combination with Chari. Even assuming such, this rejection is still incomplete as the Examiner does not indicate which aspects of the other references are being combined with the teachings of Chari.

Furthermore, as explained above, the Examiner's reliance on Chari is misplaced. One of skill in the art would not have been motivated to "make the immunoconjugates comprising the maytansinoids synthesized by Chari" by the teachings of Chari "on the high therapeutic index afforded by maytansinoid toxins relative to chemotherapeutic agents" as stated by the Examiner. Maytansinoid toxins are among the anticancer drugs referred to in Chari (termed "chemotherapeutic agents" by the Examiner). Maytansinoids are not proteins. Thus, the

Examiner's statement concerning "the high therapeutic index afforded by maytansinoid toxins relative to chemotherapeutic agents" is illogical.

Applicants also refer to and incorporate herein the additional comments above regarding the Examiner's failure to meet two of the elements of the test for obviousness regarding Liu (1997), Iwasaki (1998), Pegram (1999), Watson (1996) and Schlom (1991). Chari does not provide the missing elements of a suggestion or motivation to combine the prior art references, or a reasonable expectation of success in combining the references.

For these reasons, neither Chari alone (as stated by the Examiner), nor Chari in combination with Liu (1997), Iwasaki (1998), Pegram (1999), Watson (1996) and Schlom (1991) (as appears to be the Examiner's intent in this rejection) make the rejected claims obvious. Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection.

D. At paragraph 8 of the Office Action, claims 93-98, 100-111, 113 and 115-119 are rejected under 35 U.S.C. §103(a) as not being patentable over Guchelaar (1994) in view of Liu (AACR 1997), Lynch (1997), Liu (EOID 1997), Iwasaki (1998) and Pegram (1999).

The Examiner states that the cited references teach the following. Guchelaar teaches a 37% response rate in treatment of lung cancer cells with taxol. Liu (AAACR) teaches a maytansinoid-based immunoconjugate was effective in killing cancer cells in mice. The teachings of the remainder of the references (including Watson, discussed by the Examiner in the text of the rejection, but not included in the list of documents being cited in the rejection) are discussed above under **B.**

The Examiner states that it would have been *prima facie* obvious to combine the administration of the maytansinoid-based immunoconjugate with taxol for the treatment of small lung carcinoma.

The Examiner explains that one of ordinary skill in the art would have been motivated to make the combination based on the various teachings of the cited documents, and "[b]ecause the mechanisms of action of these two agents differ with respect to the molecular basis by which they induce an anti-mitotic effect, it is logical to suppose that the combination of the two agents might produce some additive effect."

As discussed above under **B.**, the Examiner's supposition is merely that, a guess as to what might be the result of the interaction of the two agents. Such a statement does nothing to support the Examiner's position that there was motivation to combine the specific references cited as the basis for this rejection. The Examiner has not established that there was a teaching, suggestion or motivation to combine the cited references as a basis for the instant obviousness rejection of the claims.

Furthermore, the Examiner has not provided any support for the statement that "the binding of tubulin by taxol would not result in an antagonistic competition with maytansinoid because taxol and maytansinoid bind tubulin at separate locations." Whether or not there would be an antagonistic effect, and whether or not the two molecules bind at the same location, are not facts that are "capable of instant and unquestionable demonstration as being well-known."

The Examiner has not cited evidence to confirm that the two molecules recognize separate sites on the protein. The Examiner has provided no indication of the size of the molecules, the size of the protein they bind, the exact binding location of the molecules on the

protein or the steric effects on the protein that result from the binding of one or the other of the molecules.

The Examiner states that at page 6 that Watson teaches that vinblastine and taxol bind to tubulin at different sites. The Examiner also states that Watson teaches that the maytansinoid binding site "partially overlaps" the vinblastine binding site. It is possible that because the maytansinoid site only "partially overlaps" the vinblastine site that maytansinoid binding site also "partially overlaps" the taxol binding site. The Examiner does not provide any evidence as to whether the maytansinoid binding site and the taxol binding sites are separated.

Therefore, there would not have been a reasonable expectation of success in combining the cited references.

For the reasons, and those set forth in the discussion of the other rejections above, the Examiner has neither established a suggestion or motivation to combine the prior art references, or a reasonable expectation of success in combining the references. Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection.

E. At paragraph 9 of the Office Action, claims 93-113 and 115-119 are rejected under 35 U.S.C. §103(a) as not being patentable over Guchelaar (1994), Liu (AACR 1997), Liu (EOID 1997), Iwasaki (1998) and Pegram (1999) as applied to claims 93-98, 100-111, 113 and 115-119 above, and further in view of Schlom (1991).

The Examiner states that none of Guchelaar (1994), Liu (AACR 1997), Liu (EOID 1997), Iwasaki (1998) or Pegram (1999) teaches the administration of antibody fragments. The Examiner contends that Schlom teaches the advantages of single chain antibodies, and that it would have been obvious to combine taxol with maytansinoid-conjugated single chain antibodies

to arrive at the instant invention. The Examiner asserts that the motivation for doing so would have been the teachings of a lack of tumor penetration as a reason for reduced toxicity of immunoconjugates *in vivo*, and the teachings of Schlom regarding use of single chain antibodies in place of whole antibodies for increasing tumor penetration *in vivo*.

Applicants incorporate their arguments above concerning the failures of the cited references to make the cited claims obvious, and contend that nothing in Schlom provides the missing elements of the test for obviousness, that is, Schlom does not provide a suggestion or motivation to combine the prior art references, nor does it establish a reasonable expectation of success in combining the references. Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection.

F. At paragraph 10 of the Office Action, claims 93-97, 99, 102-110, 112 and 115-119 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-12 of U.S. Patent No. 5,208,020, in view of Siegall and Chari.

The Examiner states that Siegall teaches combination therapy with a Pseudomonas endotoxin-based immunoconjugate and paclitaxel had a greater antitumor effect in rodents than either agent alone, but that Siegall does not teach a maytansinoid-based immunoconjugate in combination with paclitaxel. The Examiner goes on to state that Chari teaches that the advantage of using protein toxins versus anticancer drugs in immunoconjugates lies in the fact that protein toxins act catalytically rather than stoichiometrically. The Examiner further states that the patent teaches maytansinoid-based immunoconjugates.

The Examiner concludes that it would have been obvious to substitute maytansinoid for the Pseudomonas endotoxin (PE40) in the Pseudomonas endotoxin-based immunoconjugate of

Siegall. The Examiner asserts that the motivation for doing so would have been the teachings of Chari on the catalytic action of protein toxins versus the stoichiometric action of anticancer drugs. The Examiner explains that one of skill in the art would have recognized that both PE40 and maytansin are protein toxins which would act catalytically within the cell, and that that they would thus have similar therapeutic potential.

The Examiner has stated on the record that Chari teaches using protein toxins is advantageous over anticancer drugs in immunoconjugates because the protein toxins act catalytically rather than stoichiometrically. As discussed above, maytansinoids are not proteins, but instead they are the anticancer drugs referred to in Chari. As such, Chari does not provide support for the Examiner's position that Chari provides a motivation to combine its teachings with that of Siegall. Indeed, if Chari teaches the advantage of using protein toxins over anticancer drugs in immunoconjugates, then the skilled artisan would not have been motivated to use a maytansinoid (an anticancer drug) in the combination taught by Siegall.

Indeed, based on the Examiner's statement, Chari et al. teaches away from the claimed combination in that, as stated by the Examiner, protein toxin-based immunoconjugates are better than anticancer drug-based immunoconjugates (such as those using maytansinoids).

As such, the claims of the pending application would not have been obvious over claims 1-12 of U.S. Patent No. 5,208,020, in view of Siegall and Chari.

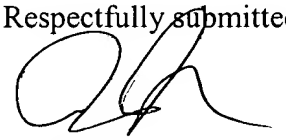
For these reasons, Applicants respectfully request reconsideration and withdrawal of this rejection.

III. Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,



SUGHRUE MION, PLLC
Telephone: (202) 293-7060
Facsimile: (202) 293-7860

WASHINGTON OFFICE
23373
CUSTOMER NUMBER

Drew Hissong
Registration No. 44,765

Date: February 14, 2005